REMARKS

Please CANCEL the response filed on March 18, 2003 and replace it with the response herein.

Reconsideration is respectfully requested.

Non-elected claims 17 and 18 have been cancelled. Claims 1-16 and 19-20 have been reiterated. Claim 21 has been amended. Claims 1-16 and 19-21 are pending.

With respect to all amendments, cancelled claims, and disclosures, Applicants have not dedicated or abandoned any unclaimed subject matter, and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Restriction Requirement

Applicants acknowledge the election of Group I, claims 1-16 and 19-20. Applicants thank the Examiner for including claim 21 in Group I.

Claim Objections

The Examiner has objected to claim 21 since claim 21 is followed by the number "20." The Examiner requests that Applicants delete claim 21.

Claim 21 has been amended to remove "20." from the claim as requested by the Examiner. Since this ground for objection is now moot, and Applicants respectfully request that the objection be withdrawn.

Information Disclosure Statement

The Examiner has notified Applicants that a number of references have not been considered, since no references were apparently found with the applications. The Examiner requests that Applicants submit copies of the references listed in the IDS for the Examiner's review.

In the response filed **March 18, 2003**, Applicants submitted a copy of the original Information Disclosure Statement along with courtesy copies of the references cited therein. Applicants respectfully request consideration of the references in the original Information Disclosure Statement.

Rejection under 35 U.S.C. §102(b)

Claims 1-16 and 19 have been rejected under 35 U.S.C. §102(b) over WO 97/41824 (Davidson et al.).

Claims 1-16 and 19

Claim 1 is directed to "a modified antiangiogenic peptide comprising a reactive group which reacts with amino groups, hydroxyl groups, or thiol groups on blood components to form stable covalent bonds wherein said reactive group is selected from the group consisting of succinimidyl and maleimido groups." Claims 2-6 depend from claim 1. Claim 7 is directed to "a composition comprising a derivative of kringle 5 peptide or analog thereof, said derivative comprising a reactive group which reacts with amino groups, hydroxyl groups or thiol groups on blood components to form stable covalent bonds wherein said reactive group is selected from the group consisting of succinimidyl and maleimido groups for use in a method of treating angiogenesis in a human." Claims 8-9 depend from claim 7. Independent claim 10 is directed to "a derivative of a kringle 5 peptide, said derivative comprising a maleimido group which reacts with a thiol group on human serum albumin to form a covalent bond." Claims 11-12 depend from claim 10. Independent claim 13 is directed to "a composition comprising a derivative of an anti-angiogenic peptide, said derivative comprising a maleimido group which reacts with a thiol group on human serum albumin to for a covalent bond for use in a method of treating angiogenesis in a human." Claims 14-16 depend from claim 13. Independent claim 19 is directed to "a modified kringle 5 peptide selected from the group consisting of" a number of different modified peptides.

The Cited Reference

Davidson et al. disclose mammalian kringle 5 fragments and fusion proteins. The reference discloses forming salts of the kringle 5 proteins and peptides, not a modified antiangiogenic peptide, composition, or kringle 5 peptide "comprising a reactive group" as required by the claims. Further, the reference discloses using maleic acid and succinic acid, not covalently linked maleimido or succinimidyl reactive groups. Davidson et al. only disclose covalently modified kringle 5 sequences have an amino-protecting group and a carboxy-protecting groups, none of which are maleimido or succinimidyl groups and none of which are reacting groups.

The Examiner's Rejection

The Examiner states that Davidson et al. teach a pharmaceutically acceptable salt of a kringle 5 peptide derivative (page 21) wherein the salt is formed by the use of maleic acid and succinic acid and wherein the pharmaceutically acceptable salt of a kringle 5 peptide derivative is used for inhibiting angiogenesis and treating angiogentic diseases (abstract pages 2-3). The Examiner erroneously alleges that Davidson et al. teach a modified antiangiogenic peptide with a reactive group, instead of a salt, as disclosed by the reference. Further, the Examiner asserts that the reference teaches that the reactive groups are succinimidyl or maleimido, even though the reference only disclosed maleic acid and succinic acid salts. Finally, the Examiner asserts that Davidson et al. teach the peptide sequences SEQ ID NO: 8, 11, 13, and 15 of claims 5-6, 11,12, 15,16, and 19.

The Cited Reference Distinguished

In order to anticipate under § 102, every element of the claimed invention must be identically shown in a single reference. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). WO 97/41824 fails to anticipate the cited reference, since the reference fails to teach multiple elements of the claims.

First, Davidson fails to disclose maleimido or succinimidyl reactive groups. The Examiner erroneously alleges that Davidson's maleic acid and succinic acid salts constitute maleimido or succinimidyl reactive groups. The maleic and succinic acid salts of peptides taught by Davidson et al., however, are not reactive groups. The salts disclosed by Davidson et al. instead are peptides with maleic and succinic ions in electrostatic association with the peptide. Thus, in the salt form of a peptide, the maleic group or succinic group is a counter-ion in relation with a positively charged group of the peptide. The maleic group or succinic acids of Davidson et al. are not covalently linked to the peptide, and cannot covalently bond a blood component to the peptide to form a conjugate. Furthermore, the maleic and succinic ions are not reactive groups that react with amino groups, hydroxyl groups, or thiol groups. The maleic and succinic ions most certainly do not form stable covalent bonds with blood components.

Second, the reference fails to teach reactive groups that react with amino groups, hydroxyl groups, or thiol groups on blood components, as required by the claims. The maleic acid and succinic acid disclosed by Davidson are only counter-ions, and not reactive groups. While the reference discloses covalently linked N-protecting or carboxy-protecting groups (see

page 9, line 37 to page 12, line 7), none are reactive groups, since the protecting groups are intended to protect the sequence and not to react with amino groups, hydroxyl groups, or thiol groups on blood components.

Third, in addition to being salts and not reactive groups, the maleic acid and succinic acid salts disclosed by Davidson et al. are chemically distinct from the claimed maleimido and succinimidyl reactive groups. The maleic acid and succinic acid disclosed by Davidson have two oxygen atoms instead of a nitrogen. Moreover, unlike the maleimido and succinimidyl reactive groups, the maleic acid and succinic acid counter-ions are not cyclic compounds.

Fourth, Davidson et al. fail to teach or suggest to that the reactive groups of the peptides, compositions, and modified kringle 5 peptides form stable covalent bonds with blood components, as required by the claims. Davidson et al. disclose only two methods of forming conjugates: "gene therapy" (see page 30, lines 22-30 and page 33, lines 4-6), and chemical well-known techniques (see page 35, lines 20-32). Davidson et al. teach that gene therapy generates fusion proteins, not peptides comprising a succinimidyl or maleimido reactive group. Davidson et al. fail to teach gene therapy fusion proteins comprising a reactive group which reacts with amino groups, hydroxyl groups, or thiol groups. Moreover, the "chemical well-known techniques" disclosed by Davidson et al. include glutaraldehyde, diazotized benzidine, carbodiimides and p-benzoquinone for cross-reacting with the protein and the kringle 5 sequence. Davidson et al. fails to disclose succinimidyl or maleimido reactive groups. The disclosed agents are not first stably attached to the kringle 5 peptides and then allow for reacting with a blood component, which differs considerably from teaching of the present invention. The agents disclosed by Davidson et al. only attach lysine residues of both the kringle 5 sequence and the protein, while reactive groups of the claimed invention react with amino groups, hydroxyl groups, or thiol groups on blood components. Furthermore, the agents disclosed by Davidson et al. only react *in vitro*, while the conjugates of the claimed invention can be made both *in vivo* and *ex vivo*.

Finally, the free kringle 5 fragments taught by Davidson et al. have the *opposite* therapeutic application to the present invention. The conjugates disclosed in Davidson et al. are intended for making antibodies or for purification purposes (see page 35, lines 14-26), not for administration for medical treatment. Davidson et al. disclose that combining the free kringle 5 fragments with a sustained-release matrices is an alternative to administering free kringle 5

fragments to (see page 22, lines 13-27). Sustained release matrices, however, slowly release the kringle 5 fragments. Unlike Davidson et al., the modified peptides of the present invention are covalently attached to blood component and the resulting conjugate provides the therapeutic efficacy and the long lasting effect, not a slowly diminishing effect.

In view of the above arguments, the cited reference fails to anticipate the claimed invention. Applicants respectfully request that this ground for rejection be withdrawn.

Rejection under 35 U.S.C. §102(e)

Claims 1-4, 6-10, 12-14, 16, and 19 have been rejected under 35 U.S.C. §102(e) as being anticipated by Davidson et al. (U.S. Patent No. 6,057,122 filed May 5, 1997, issued May 2, 2000).

Claims 1-4, 6-10, 12-14, 16, and 19

Claim 1 is directed to "a modified antiangiogenic peptide comprising a reactive group which reacts with amino groups, hydroxyl groups, or thiol groups on blood components to form stable covalent bonds wherein said reactive group is selected from the group consisting of succinimidyl and maleimido groups." Claims 2-4 and 6 depend from claim 1. Claim 7 is directed to "a composition comprising a derivative of kringle 5 peptide or analog thereof, said derivative comprising a reactive group which reacts with amino groups, hydroxyl groups or thiol groups on blood components to form stable covalent bonds wherein said reactive group is selected from the group consisting of succinimidyl and maleimido groups for use in a method of treating angiogenesis in a human." Claims 8-9 depend from claim 7. Independent claim 10 is directed to "a derivative of a kringle 5 peptide, said derivative comprising a maleimido group which reacts with a thiol group on human serum albumin to form a covalent bond." Claim depends from claim 10. Independent claim 13 is directed to "a composition comprising a derivative of an anti-angiogenic peptide, said derivative comprising a maleimido group which reacts with a thiol group on human serum albumin to for a covalent bond for use in a method of treating angiogenesis in a human." Claim 14 depends from claim 13. Independent claim 19 is directed to "a modified kringle 5 peptide selected from the group consisting of" a number of different modified peptides.

The Examiner's Rejection

The Examiner alleges that Davidson et al. teach pharmaceutically acceptable salt of a kringle 5 peptide derivative (column 18 lines 5-43) wherein the salt is formed by use of maleic

acid and succinic acid and wherein the pharmaceutically acceptable salt of a kringle 5 peptide derivative is used for inhibiting angiogenesis and treating angiogenic diseases (abstract, column 2, lines 64- 67). The Examiner further alleges that 1-4, 7-10, and 13-14 teach a modified antiangiogenic kringle 5 peptide with a reactive group (succinimidyl or maleimido) as in Davidson et al., for the treatment of angiogenic diseases. In addition, the Examiner asserts that Davidson et al. teach peptide sequences of SEQ ID NOS: 15-16 of claims 6, 12, 16, and 19 (Davidson et al., SEQ ID NO:18 and example 4, column 36).

The Cited Reference

As in WO 97/41824, Davidson et al. (U.S. Patent No. 6,057,122) discloses mammalian kringle 5 fragments and fusion proteins. Davidson et al. discloses forming salts of the kringle 5 proteins and peptides, not a modified antiangiogenic peptide, composition, or kringle 5 peptide "comprising a reactive group" as required by the claims. Further, the reference discloses using maleic acid and succinic acid, not covalently linked maleimido or succinimidyl reactive groups. Davidson et al. only disclose covalently modified kringle 5 sequences have an amino-protecting group and a carboxy-protecting groups, none of which are maleimido or succinimidyl groups and none of which are reacting groups.

The Cited Reference Distinguished

In order to anticipate under § 102, every element of the claimed invention must be identically shown in a single reference. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). U.S. Patent No. 6,057,122 to Davidson et al. fails to anticipate the cited reference, since the reference fails to teach multiple elements of the claims.

First, as stated in the previous rejection and reiterated here, Davidson fails to disclose maleimido or succinimidyl reactive groups. The Examiner erroneously alleges that Davidson's maleic acid and succinic acid salts constitute maleimido or succinimidyl reactive groups. The maleic and succinic acid salts of peptides taught by Davidson et al., however, are not reactive groups. The salts disclosed by Davidson et al. instead are peptides with maleic and succinic ions in electrostatic association with the peptide. Thus, in the salt form of a peptide, the maleic group or succinic group is a counter-ion in relation with a positively charged group of the peptide. The maleic group or succinic acids of Davidson et al. are not covalently linked to the peptide, and cannot covalently bond a blood component to the peptide to form a conjugate. Furthermore, the maleic and succinic ions are not reactive groups that react with amino groups, hydroxyl groups,

or thiol groups. The maleic and succinic ions most certainly do not form stable covalent bonds with blood components.

Second, like WO 97/41824 to Davidson, U.S. Patent No. 6,057,122 to Davidson et al. fails to teach reactive groups that react with amino groups, hydroxyl groups, or thiol groups on blood components, as required by the claims. The maleic acid and succinic acid disclosed by Davidson are only counter-ions, and not reactive groups. While the reference discloses covalently linked N-protecting or carboxy-protecting groups (see page 9, line 37 to page 12, line 7), none are reactive groups, since the protecting groups are intended to protect the sequence and not to react with amino groups, hydroxyl groups, or thiol groups on blood components.

Third, the maleic acid and succinic acid salts disclosed by Davidson et al. are chemically distinct from the claimed maleimido and succinimidyl reactive groups. The maleic acid and succinic acid disclosed by Davidson have two oxygens instead of a nitrogen. Moreover, unlike the maleimido and succinimidyl reactive groups, the maleic acid and succinic acid counter-ions are not cyclic compounds.

Fourth, U.S. Patent No. 6,057,122 to Davidson et al. fails to teach or suggest to that the reactive groups of the peptides, compositions, and modified kringle 5 peptides form stable covalent bonds with blood components, as required by the claims. Davidson et al. disclose only two methods of forming conjugates: "gene therapy" (see page 30, lines 22-30 and page 33, lines 4-6), and chemical well-known techniques (see page 35, lines 20-32). Davidson et al. teach that gene therapy generates fusion proteins, not peptides comprising a succinimidyl or maleimido reactive group. Davidson et al. fail to teach gene therapy fusion proteins comprising a reactive group which reacts with amino groups, hydroxyl groups, or thiol groups. Moreover, the "chemical well-known techniques" disclosed by Davidson et al. include glutaraldehyde, diazotized benzidine, carbodiimides and p-benzoquinone for cross-reacting with the protein and the kringle 5 sequence. Davidson et al. fails to disclose succinimidyl or maleimido reactive groups. The disclosed agents are not first stably attached to the kringle 5 peptides and then allow for reacting with a blood component, which differs considerably from teaching of the present invention. The agents disclosed by Davidson et al. only attach lysine residues of both the kringle 5 sequence and the protein, while reactive groups of the claimed invention react with amino groups, hydroxyl groups, or thiol groups on blood components. Furthermore, the agents

disclosed by Davidson et al. only react *in vitro*, while the conjugates of the claimed invention can be made both *in vivo* and *ex vivo*.

Finally, the free kringle 5 fragments taught by Davidson et al. have the *opposite* therapeutic application to the present invention. The conjugates disclosed in Davidson et al. are intended for making antibodies or for purification purposes (see page 35, lines 14-26), not for administration for medical treatment. Davidson et al. disclose that combining the free kringle 5 fragments with a sustained-release matrices is an alternative to administering free kringle 5 fragments to (see page 22, lines 13-27). Sustained release matrices, however, slowly release the kringle 5 fragments. Unlike Davidson et al., the modified peptides of the present invention are covalently attached to blood component and the resulting conjugate provides the therapeutic efficacy and the long lasting effect, not a slowly diminishing effect.

In view of the above arguments, the cited reference fails to anticipate the claimed invention. Applicants respectfully request that this ground for rejection be withdrawn.

Conclusion

In light of the above amendments and remarks, Applicant believes that this case is now in condition for allowance. Should there be any remaining issues that remain unresolved, the Examiner is encouraged to telephone the undersigned.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **500862001400**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: April 2, 2003

By: Michael R Ward

Michael R. Ward
Registration No. (38,651)

Morrison & Foerster LLP
425 Market Street
San Francisco, California 94105-2482
Telephone: (415) 268-6237
Facsimile: (415) 268-7522